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Effects of Exercise and Caloric Restriction on Insulin Resistance and Cardiometabolic Risk Factors in Older Obese Adults—A Randomized Clinical Trial

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Background. The prevalence of insulin resistance, metabolic syndrome, and cardiovascular disease is greatest in older obese patients, and effective evidence-based treatment strategies are lacking.

Methods. A prospective controlled study was conducted on 24 older (65.5 ± 5.0 years) obese (body mass index, 34.3 ± 5.2 kg/m^2) adults with clinically diagnosed metabolic syndrome. We examined the effect of exercise alone (EX) or exercise combined with moderate caloric restriction (−500 kcal, EX + CR) on metabolic and cardiovascular risk factors. Measures of insulin sensitivity assessed by euglycemic hyperinsulinemic clamp and by oral glucose tolerance test, lipid profiles, blood pressure, body composition, abdominal fat, and aerobic capacity were all obtained before and after the interventions.

Results. Both groups experienced significant weight loss, but the reduction was greater in the EX + CR group than in the EX group (−6.8 ± 2.7 kg vs −3.7 ± 3.4 kg, respectively, $p = .02$). Both interventions improved insulin sensitivity (2.4 ± 2.4 mg/kg FFM/min and 1.4 ± 1.7 mg/kgFFM/min, respectively, $p < .001$) and indices of metabolic syndrome (systolic/diastolic blood pressure, waist circumference, glucose, and triglycerides; $p < .05$). High-density lipoprotein levels remained unchanged. Total abdominal, subcutaneous, and visceral fat; aerobic capacity; and total and low-density lipoprotein cholesterol were also improved. With the exception of weight loss and subcutaneous fat, there was no difference in the magnitude of improvement between the interventions.

Conclusion. These data suggest that exercise alone is an effective nonpharmacological treatment strategy for insulin resistance, metabolic syndrome, and cardiovascular disease risk factors in older obese adults.

Key Words: Aging—Obesity—Diabetes—Impaired glucose tolerance.

A recent analysis of the data set from the Third National Health and Nutrition Examination Survey suggests that 33% of U.S. adults who are 50 years of age or older and have impaired glucose tolerance also have metabolic syndrome (1). Of interest, the age-specific prevalence of metabolic syndrome increases dramatically, from just more than 12% among individuals in their thirties to 20% among those in their forties, 35% among those in their fifties, and 45% in those 60 years and older (2). The metabolic syndrome is a cluster of physiological and metabolic measures that collectively confer increased risk for cardiovascular disease and are strongly associated with central adiposity and insulin resistance. Specific definitions are provided by the 2001 National Cholesterol Education Program (NCEP), the International Diabetes Federation, and the World Health Organization (3). Central adiposity is a key component of the syndrome, and increases in abdominal fat are well described with advancing age (4,5). Exercise can profoundly change body composition, often independent of caloric restriction, and can preferentially reduce abdominal and visceral fat (6–10). Moreover, data from the Diabetes Prevention Program (11) showed greater benefit for the lifestyle intervention compared with drug therapy (metformin), and this benefit was greatest in those older than 60 years. Support for the effectiveness of exercise on cardiovascular disease risk factors is evident from the Senior Hypertension and Physical Exercise study, which has shown that exercise reduces total and abdominal body fat, increases muscle mass, and ameliorates the risk factors that make up the metabolic syndrome (12). Data from the Cooper Clinic further underscore the importance of fitness in the health of older adults and show that if fit, obese individuals have a lower risk of all-cause mortality than unfit, normal-weight, or lean individuals (13).

Diet-induced weight loss can also reduce health risk, but older adults tend to lose more muscle in response to calorie-restricted diets, compared with middle-aged adults (14,15). The addition of exercise may counter this loss of muscle, but the extent to which this is true in older obese adults is less clear. The specific aims of this study were to examine the effect of exercise alone or exercise combined with moderate caloric restriction on major cardiovascular disease risk factors, notably the criterion that defines the metabolic syndrome, and to test if the combined intervention has an added benefit over exercise alone in older obese men and women.

Methods

Participants

A total of 24 older (65.5 ± 5.0 years) participants (9 males and 15 females) who were weight stable (<2-kg weight change in the previous 6 months), sedentary (<20 minutes' exercise twice per week), and obese (body mass index [BMI], 30–40 kg/m^2) were recruited to participate in one of the two interventions. The participants were randomly assigned to exercise alone (EX, n = 12, 64 ± 2 years) or exercise combined with a 500-kcal reduction in energy intake (EX + CR, n = 12, 67 ± 1 years). All the patients met the criteria for metabolic syndrome as determined by guidelines from the 2001 NCEP (Adult Treatment Panel III). All participants had fasting glucose values less than 126 mg/dL on screening, 5 had glucose values less than 140 mg/dL at the 2-hour time point during a 75-g oral glucose tolerance test (OGTT; 4 EX and 1 EX + CR), 11 had glucose values less than 200 mg/dL (3 EX and 8 EX + CR), and 8 had glucose values more than 200 mg/dL but less than 290 mg/dL (5 EX and 3 EX + CR) (16). Resting blood pressure was obtained in a seated position and was based on the average measure obtained for 5 days of the week before and after the interventions. Exclusion criteria included evidence of overt type 1 diabetes mellitus or treated type 2 diabetes mellitus (T2DM), acute or chronic disease (cardiovascular, cerebrovascular, liver, renal, hematological, thyroid, or cancer), smoking, and medications affecting metabolism. Participants were not taking blood pressure or diabetes medications. All women were postmenopausal for more than 1 year and had not been on hormone replacement therapy for at least 1 year prior to enrollment. Participants gave their written informed consent to participate in this study in accordance with the institutional guidelines for the protection of human participants.

Exercise Training Program

All exercise training was supervised by an exercise physiologist and conducted in the General Clinical Research Center (GCRC). Maximal oxygen consumption (VO_{2max}) was determined by an incremental, graded treadmill exercise test. Intensity for the exercise training program was calculated from the maximum heart rate achieved during the treadmill test.

Participants exercised for 50–60 min/d, 5 d/wk, for 12 weeks. The exercise consisted of walking on a treadmill and/or pedaling a cycle ergometer, with more than 75% of their effort spent on the treadmill. The initial exercise sessions were performed at between 60% and 65% of the heart rate maximum (HR_{max}), and the intensity was gradually increased so that by Week 4, the participants were exercising at 80%–85% HR_{max} (~70% VO_{2max}). Target heart rates were monitored using telemetry (Polar Electro, Inc., Woodbury, NY). The VO_{2max} tests were performed at baseline and at 4, 8, and 12 weeks of exercise to monitor progress and adjust training intensity.

Diet Monitoring

Energy intakes were estimated using the Harris Benedict equation and an activity factor of 1.3 (17). In the exercise-only group, participants were counseled not to alter their energy intake. In the EX + CR group, participants were required to reduce their energy intake by 500 kcal/d. The nutritionist met weekly with the participants to ensure that they understood and maintained their appropriate diet. Each participant completed two 3-day food records before the intervention and again during Weeks 1, 3, 6, 9, and 12. Diet composition was determined using the Nutritionist IV software program (N-Squared Computing, San Bruno, CA). Body weight was measured once each week during the study period to monitor compliance.

Body Composition

Body density was determined by hydrostatic weighing, and fat mass and fat-free mass were estimated using the equation of Siri as previously described (9). Computed axial tomography (Picker PQ6000 Scanner; Marconi/Picker, Highland Heights, OH) was used to measure the distribution of cross-sectional abdominal fat depots (total abdominal, visceral, and subcutaneous), as previously described (9).

Measures of Insulin Resistance

Euglycemic hyperinsulinemic clamps and an OGTT were used to assess insulin resistance. Participants resided in the GCRC for 3 days and nights prior to all metabolic measures. During this time, activity and diet were under tight control. Postintervention clamps were performed approximately 16 hours after the last exercise session. All procedures were performed in the morning after an overnight fast. The clamps were performed as described previously (18,19). A primed-continuous infusion of insulin (40 mU/m^2/min) was begun and maintained for 120 minutes. Plasma glucose was clamped at 5 mmol/L during hyperinsulinemia by a variable-rate glucose (20% dextrose) infusion. Tritiated glucose (NEN-Dupont, Boston, MA) was used to determine endogenous glucose suppression, as previously described (8,20). Total glucose disposal rates (GDRs) and glucose infusion rates (GIRs) are reported for the last 30 minutes of the clamp. Areas under the glucose and insulin response curves following the OGTT were determined using the trapezoid model. The product of the Glucose Area Under the Curve (AUC) × Insulin AUC was calculated as an index of insulin action as previously described (9).

Statistical Analyses

A Student's t test was used to evaluate baseline differences between groups. Changes in variables from baseline to the

Table 1. Participant Characteristics Before and After the Exercise or Diet Interventions

	EX Group		EX + CR Group			
Characteristics	Preintervention	Postintervention	Preintervention	Postintervention	Within-Group *p* Value	Between-Group *p* Value
Body composition						
Weight (kg)	99.7 ± 15.7	95.9 ± 14.6	94.9 ± 16.5	88.0 ± 14.5	<.001	.02
BMI (kg/m^2)	35.3 ± 5.8	34.0 ± 5.8	33.7 ± 4.7	31.3 ± 4.3	<.001	.01
Fat mass (kg)	41.6 ± 11.3	37.1 ± 11.4	37.6 ± 9.8	31.6 ± 8.7	<.001	.47
Fat-free mass (kg)	57.7 ± 9.6	58.5 ± 10.5	57.7 ± 11.7	55.8 ± 11.3	.48	.11
Waist circumference (cm)	118.3 ± 12.7	112.7 ± 11.9	113.6 ± 12.7	107.1 ± 11.7	<.001	.62
Waist-to-hip ratio	0.96 ± 0.06	0.94 ± 0.07	0.96 ± 0.06	0.96 ± 0.04	.37	.25
Visceral fat (cm^2)	192.3 ± 104.3	158.4 ± 87.0	236.8 ± 71.6	197.0 ± 73.6	<.001	.85
Subcutaneous fat (cm^2)	383.4 ± 106.4	347.8 ± 94.2	426.7 ± 121.7	360.4 ± 130.3	<.001	.03
Blood pressure						
Systolic (mm Hg)	135.6 ± 11.2	121.1 ± 11.2	134.2 ± 11.6	119.7 ± 8.1	<.001	.99
Diastolic (mm Hg)	81.6 ± 11.2	71.6 ± 9.6	81.3 ± 4.1	72.2 ± 5.1	<.001	.77
Insulin resistance						
Fasting glucose (mg/dL)	106.6 ± 10.8	103.0 ± 9.3	107.1 ± 6.6	103.5 ± 6.6	<.03	.98
Fasting insulin (pmol/L)	107.9 ± 48.8	84.6 ± 26.5	108.4 ± 30.8	79.2 ± 20.8	<.001	.63
GDR (mg/kg FFM/min)	5.0 ± 1.9	6.4 ± 1.8	4.2 ± 1.8	6.6 ± 2.9	<.001	.70
GIR (mg/kg FFM/min)	2.2 ± 0.9	3.1 ±1.3	1.5 ± 0.7	2.6 ± 1.2	<.001	.64
OGTT (AU)	28.0 ± 30.3	16.5 ± 19.2	29.4 ± 15.9	16.7 ± 18.7	<.001	.85
Lipid profile						
Triglycerides (mg/dL)	169.2 ± 62.5	134.1 ± 37.5	171.1 ± 52.6	117.0 ± 48.2	<.001	.31
Cholesterol (mg/dL)	180.7 ± 37.2	161.7 ± 32.6	181.2 ± 24.0	157.1 ± 27.6	<.001	.55
HDL (mg/dL)	36.9 ± 8.3	37.5 ± 7.6	34.2 ± 5.7	33.4 ± 7.8	.90	.48
LDL (mg/dL)	109.2 ± 28.4	101.5 ± 23.4	118.2 ± 17.3	104.2 ± 19.0	<.004	.37
Aerobic fitness						
VO_{2max} (L/min)	2.0 ± 0.5	2.3 ± 0.6	2.0 ± 0.5	2.2 ± 0.5	<.001	.56

Notes: Data are means ± standard deviation (EX, $n = 12$; EX + CR, $n = 12$).

AU = arbitrary units derived from the product of the areas under the glucose and insulin response curves (×10^7); BMI = body mass index; EX = exercise alone; EX + CR = exercise plus caloric restriction; GDR = glucose disposal rate; GIR = glucose infusion rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; OGTT = oral glucose tolerance test.

end of the intervention were determined by two-way time-by-group repeated measures analysis of variance. The relationship between dependent and independent variables was based on univariate correlation analysis using the differences before and after the intervention. Multiple regression analysis was used to evaluate the independent effects of fitness and insulin sensitivity on the measured risk factors. The data were analyzed using the StatView II statistical package (Abacus Concepts, Berkley, CA). Data are expressed as means ± standard deviation; $p < .05$ was considered significant.

Results

Exercise and Diet

There were no between-group differences at baseline for exercise capacity, caloric intake, body composition, blood pressure, insulin resistance, or lipids (Table 1). Compliance with the program was more than 94% for both groups, and average weekly attendance was 4.7 ± 0.3 d/wk and 4.7 ± 0.2 d/wk for the EX and EX + CR groups, respectively. Both interventions led to a significant and similar improvement in aerobic capacity ($p < .001$; Table 1). As planned, participants in the EX + CR group consumed fewer calories (1,303 ± 210 kcal/d) than those in the EX group (2,141 ± 1,338 kcal/d) ($p < .05$).

Body Composition and Abdominal Fat

Weight loss was 3.8% and 7.4% in the EX and EX + CR groups, respectively, and as expected, the EX + CR group lost more weight than the EX group ($p = .02$; Table 1). Importantly, fat-free mass was not significantly altered in either group, despite the tendency toward loss of muscle mass during EX + CR ($p = .11$). Abdominal adiposity was reduced in both groups ($p < .001$), but there was no difference between groups following the trials ($p = .62$). These observations were confirmed by computed tomography scanning, which showed that total abdominal fat and visceral and subcutaneous fat depots were reduced following the two interventions ($p < .001$).

Insulin Resistance

All measures of insulin resistance were improved following the completion of both intervention programs ($p < .001$; Table 1). There was a 20% change in the GDR after the EX trial and a 28% change after the EX + CR trial. Based on the OGTT, insulin sensitivity was improved by 31% after the EX intervention and by 30% following the EX + CR intervention. Fasting insulin decreased by 27% following the EX intervention and by 37% after the EX + CR intervention. The improvement in glucose tolerance after the respective interventions was equally spread between the two groups.

Table 2. Correlation Matrix Constructed From Absolute Changes in the Cluster of Risk Factors that Comprise Metabolic Syndrome and From Changes in Body Composition and Fitness

	SBP	DBP	TG	HDL	Glucose	WC
Weight (kg)	.10	.13	.10	.17	.29	.44*
Visceral fat (cm^2)	.52*	.08	.13	.12	.54*	.32
Subcutaneous fat (cm^2)	.01	.34	.29	.09	.09	.48†
VO_{2max} (L/min)	.19	.18	.28	.47*	.11	.02

Notes: DBP = diastolic blood pressure; HDL = high-density lipoprotein; SBP = systolic blood pressure; TG = triglycerides; WC = waist circumference.

* Significant correlation between body weight and waist circumference; visceral fat and systolic blood pressure; and fasting glucose, VO_{2max}, and HDL ($p < .05$).

† Significant correlation between subcutaneous fat and waist circumference ($p < .01$).

Three participants in the EX group moved to normal glucose tolerance (NGT), whereas four in the EX + CR group moved to NGT. Three participants in the EX group moved from T2DM to impaired glucose tolerance (IGT), and likewise, three participants in the EX + CR group moved from T2DM to IGT.

Table 3. Correlation Matrix Derived From Absolute Changes in Insulin Resistance After the Intervention and From Absolute Change in Metabolic Variables

	ΔGDR		ΔGIR		ΔOGTT	
Δ	*R*	*p* Value	*R*	*p* Value	*R*	*p* Value
Weight (kg)	.43	.04	.39	.06	.46	.03
BMI (kg/m^2)	.17	.29	.24	.25	.21	.37
Fat mass (kg)	.01	.95	.11	.60	.03	.90
Fat-free mass (kg)	.13	.54	.06	.77	.14	.52
Waist circumference (cm)	.10	.65	.01	.96	.4	.07
Waist-to-hip ratio	.14	.54	.01	.98	.10	.65
Visceral fat (cm^2)	.48	.04	.46	.05	.52	.05
Subcutaneous fat (cm^2)	.18	.48	.01	.98	.14	.60
Systolic pressure (mm Hg)	.03	.88	.12	.58	.16	.48
Diastolic pressure (mm Hg)	.01	.96	.16	.47	.18	.44
Fasting glucose (mg/dL)	.31	.14	.44	.03	.7	.0003
Fasting insulin (pmol/L)	.27	.21	.26	.23	.6	.003
Triglycerides (mg/dL)	.22	.30	.40	.05	.17	.44
Cholesterol (mg/dL)	.28	.19	.36	.08	.52	.01
HDL (mg/dL)	.04	.85	.11	.61	.1	.68
LDL (mg/dL)	.20	.35	.22	.29	.36	.10
VO_{2max} (L/min)	.47	.02	.57	.004	.17	.44

Note: BMI = body mass index; GDR = glucose disposal rate; GIR = glucose infusion rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; OGTT = oral glucose tolerance test.

Blood Pressure

Both groups of participants experienced a significant reduction in blood pressure following the 12-week programs ($p < .001$; Table 1). There was no significant group difference after either intervention (systolic $p = .99$, diastolic $p = .77$).

Lipid Profile

Cholesterol, triglycerides, and low-density lipoproteins (LDLs) were reduced in both groups following the respective 12-week programs ($p < .005$; Table 1). There was no significant group difference between the interventions for cholesterol, triglycerides, and LDLs. Furthermore, high-density lipoproteins (HDLs) did not significantly change after the interventions in either group ($p = .48$).

Correlation Analysis

From the six risk factors that make up the metabolic syndrome (Table 2), systolic blood pressure and glucose correlated with visceral fat, HDLs correlated with aerobic capacity, and waist circumference correlated with body weight and subcutaneous fat (Tables 2 and 3). Using univariate analysis (Table 3), the best predictor of the change in insulin resistance based on all three measures (GDRs, GIRs, and OGTT) was the change in body weight and visceral fat. In a stepwise regression analysis for GDR, GIR, and OGTT, the change in body weight was significant (GDR, 34%, $p < .007$; GIR, 31%, $p < .01$). For insulin resistance based on the OGTT, 89% of the variance could be accounted for by changes in fasting glucose (64%), waist circumference (19%), and fasting insulin (6%). Body weight did not enter this model.

Discussion

In this 12-week trial, exercise with its inherent mild weight loss had a significant beneficial impact on body composition, the risk factors associated with metabolic syndrome, and cardiovascular and metabolic disease in an older obese population. The addition of a diet-based weight loss program to the exercise intervention did not lead to greater improvements in this study. Although the exercise intervention was performed at a relatively high intensity based on each individual's aerobic capacity and was sustained for a relatively prolonged duration for each exercise session, this was nevertheless a walking program. What this highlights, in part, is the relatively low aerobic fitness of these individuals and more importantly that a walking program can bring about significant weight loss and an improvement in clinical outcomes in 12 weeks. The improvement in aerobic fitness was associated with the improvement in insulin sensitivity based on clamp measures. More than 90% of glucose disposal during a clamp is taken up by skeletal muscle. These data suggest that the central and peripheral adaptations that are reflective of increased VO_{2max} may contribute to the improvement in glucose disposal in these participants. This may occur via improved blood flow to the muscle, thus increasing insulin delivery, or enhanced muscle function leading to improved insulin signaling and glucose uptake (21,22). Collectively, these observations provide strong support for prescribing brisk, sustained walking exercise for older obese adults.

The addition of caloric restriction (500 kcal/d) to the exercise intervention was successful in generating greater weight loss, but surprisingly, this did not translate to greater improvements in the clinical measures that underpin the metabolic syndrome and presumably chronic disease risk. Although several previous studies on exercise and caloric restriction (23–30) have been published, we believe that it is important to distinguish studies of older versus younger adults and quantify the exercise sessions and the amount of caloric restriction. In some studies that have compared caloric restriction with exercise, participants often exercised three sessions per week, each session lasting around 30 minutes, with minimal change in body weight (26,28). Although exercise in these studies improved the cardiovascular profile, greater weight loss produced through dieting or a combined intervention had a superior outcome in younger (29,30), older (27,28), or mixed–age group populations (25,26). However, mechanisms of energy balance are dysregulated in old age, and the response to a negative energy balance is attenuated (31,32). Consequently, older adults experience greater loss of muscle mass with intentional caloric restriction compared with younger adults (14,15). Weiss and colleagues have shown in older men and women that muscle mass and absolute work capacity decrease in response to 12 months of caloric restriction but not in response to a similar amount of weight loss induced by exercise (33). The loss of muscle with advancing aging is clinically known as sarcopenia and is strongly related to impaired mobility, increased mortality and morbidity, and lower quality of life (34). Although both groups of participants in our study preserved muscle mass, we did observe a trend for a greater loss of muscle in the caloric restriction group (~4%, $p = .11$). These observations suggest that there is a need for caution and a careful assessment of the risk or benefit when prescribing diet-induced weight loss in the elderly.

It is well established that aging is associated with an increased accumulation of truncal fat, and studies have previously shown that there is a preferential loss of fat from the central regions of the body with exercise training in older adults (7–9,27). In the present study, the reduction in visceral fat was associated with improvements in insulin resistance and was also correlated with the change in fasting glucose. Recent reports and reviews conclude that independent of total weight loss, or even reductions in waist circumference, reduced visceral fat contributes to reduced cardiovascular risk (6,10,24). We observed that the improvement in metabolic syndrome and insulin resistance was comparable for both interventions. The reduction in visceral fat was also similar in both groups, whereas the reduction in total body weight and subcutaneous fat was greater during the exercise or caloric restriction trial. Our correlation data underscore the importance of fitness and weight loss in improving insulin resistance, possibly through exercise-induced weight loss–associated mobilization of visceral fat stores and improved skeletal muscle insulin sensitivity. Data from this study suggest that there may be a threshold for improving metabolic syndrome, and this can be reached by exercise alone or by exercise plus caloric restriction. Fitness had a very strong correlation with insulin sensitivity (Table 3), and this observation supports recently published data that fitness is a strong and independent predictor of all-cause mortality in adults 60 years or older (13). The combined effects of reduced visceral fat and improved fitness appear to be powerful contributors to reduced cardiometabolic health risk.

The interventions produced marked improvements in resting blood pressure. These data are consistent with the observations of Dengel and colleagues who reported improved blood pressures after exercise training with and without weight loss in older men (28). The change in systolic blood pressure correlated with the reduction in visceral fat. The mechanistic link between systolic blood pressure and visceral fat may reside with inflammatory cytokines such as tumor necrosis factor α and interleukin-6, which are known to increase with advancing age (35). These cytokines together with adhesion molecules such as vascular adhesion molecule-1 and intercellular adhesion molecule-1 may contribute to increased endothelial activation and hypertension (36). It is possible that the decrease in visceral fat contributed to a reduction in proinflammatory cytokines, thereby removing the stimulus for endothelial dysfunction and hypertension.

One limitation of this study is the relatively small number of participants studied. It is possible that with additional participants, some of the group differences may have reached statistical significance. However, the between-group p values shown in Table 1 suggest that these numbers would have to be increased substantially to attempt to demonstrate such an effect. Furthermore, it is likely that these cardiometabolic benefits would require even greater caloric restriction with a subsequent greater weight loss and an increased likelihood of losing muscle mass. In addition, participants in this study were evaluated when they were fully trained, and so the effects of exercise were maximized. It is worth considering that because the effects of exercise are short lived, the EX + CR group may have had a more long-lived benefit because the known effects of caloric restriction on insulin resistance tend to persist longer than exercise alone. If measures had been obtained 7–10 days after the intervention, the effect of the greater weight loss with caloric restriction may have been more evident. On the other hand, delaying the insulin sensitivity measure too long after the last exercise may result in a “de-training” effect, which would in turn mask the exercise benefit.

In conclusion, data from this study suggest that frequent habitual exercise with its inherent mild weight loss had a significant beneficial impact on body composition, the risk factors associated with metabolic syndrome, and cardiovascular and metabolic disease in an older obese population. The addition of a diet-based weight loss program to the exercise intervention did not lead to greater improvements in these older obese adults. Although it would seem that exercise alone may be adequate to achieve significant improvements in health risk, one must also consider that the effects of exercise are short lived, whereas the benefits that accrue from caloric restriction may be sustainable for a longer period of time.

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